Mechanics of a Blebbing Cell

A Mathematical Model

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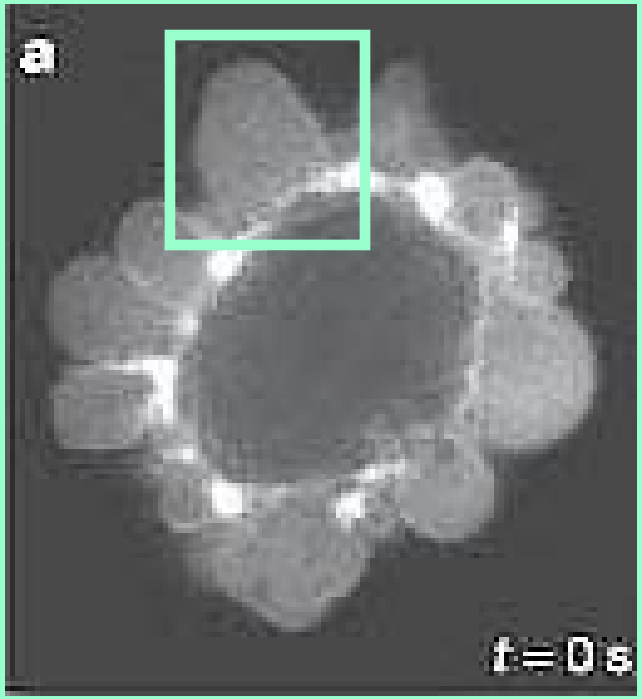
Outline

- Problem Description
- Hypothesis
- Equations
- Validation of Simulation Components
- Past Results
- Future Direction

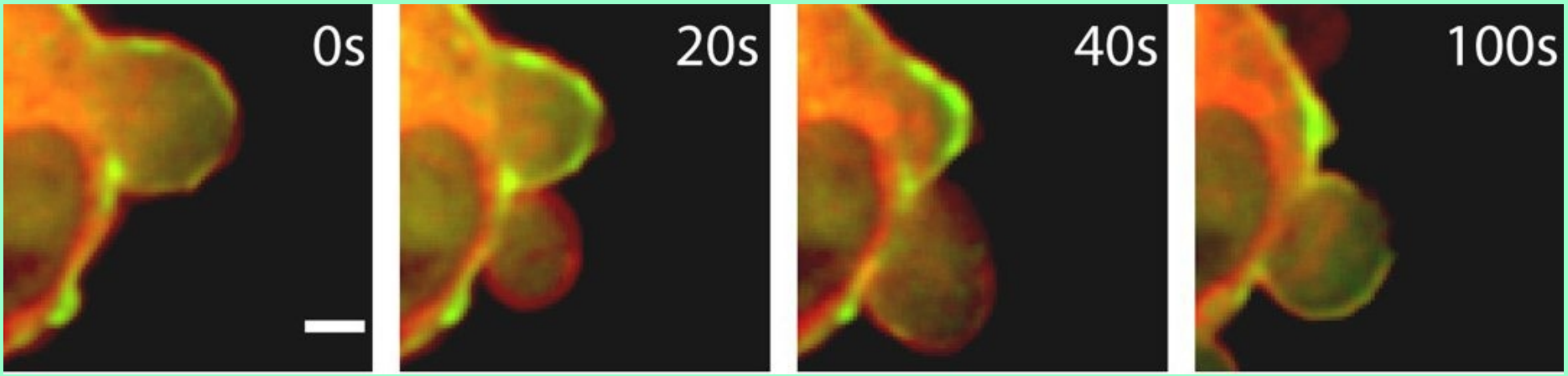
What is a Bleb?

- Balloon-like Protrusion
- Membrane separates from cortical filament network
- Cytoplasm inflates bleb
- Blebbing occurs during:
  - Cell Motility
  - Apoptosis

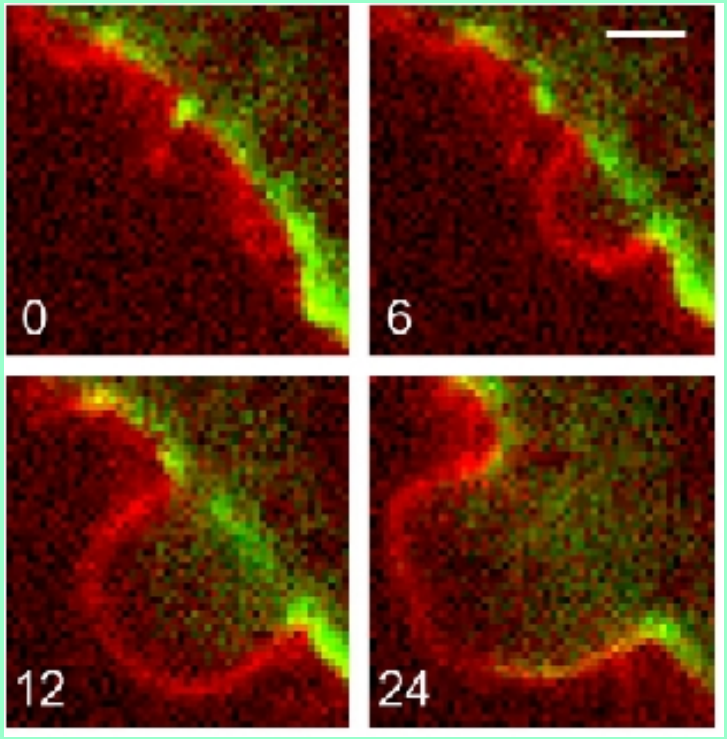


Confocal microscopy image (Charras et al. Nature, May 2005)

Stages of Blebbing



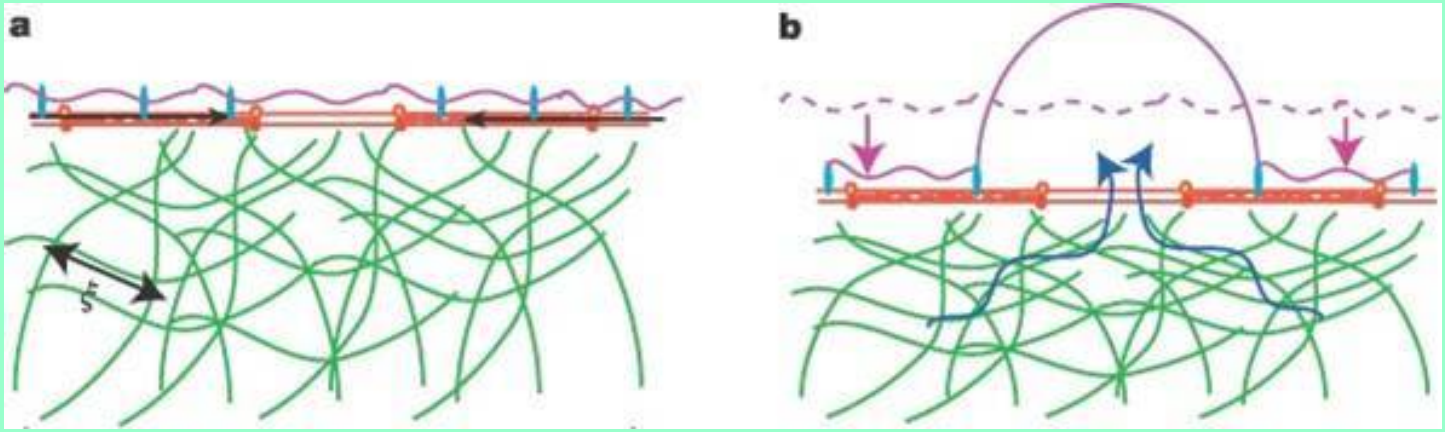
Confocal microscopy time sequence of bleb formation (Charras et al. JCB, May 2006)



Fluorescently labeled actin (green) during bleb formation (Charras et al. Nature, May 2005)

The Hypothesis

- The actin-myosin network contracts
- This force causes the release of the membrane from the filament network
- Due to pressure gradients, cytoplasm flows into the detached region forcing the membrane outward to form the bleb



Cartoon image (Charras et al. Nature, May 2005)

Fluid Equation

Navier-Stokes

$$F = ma$$

$$-\nabla p + \mu \Delta u + f = \rho \left(\frac{\partial u}{\partial t} + (u \cdot \nabla) u \right)$$

$$F_{\mathrm{Pr}essure} + F_{Viscous} + F_{Body} = F_{Inertia}$$

Steady Stokes: Inertial forces ignored due to the small scale of the cell versus the large time scale of blebbing

$$-\nabla p + \mu \Delta u + f = 0$$

Elasticity Equation

Generalized Hooke's Law: $\sigma = E\varepsilon$

σ Stress, ε Strain, E Elasticity Modulus

Equation of Motion: $ma = \sum F$

Force generated from difference in strains along length

Filaments

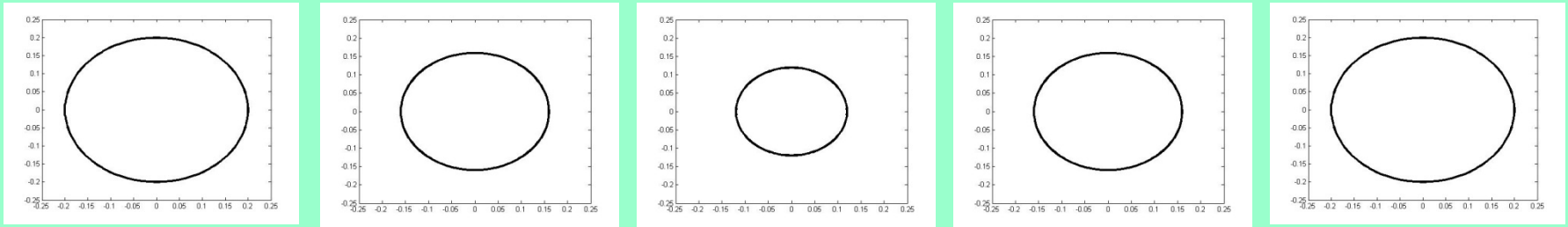
$$ma = E\varepsilon_S$$

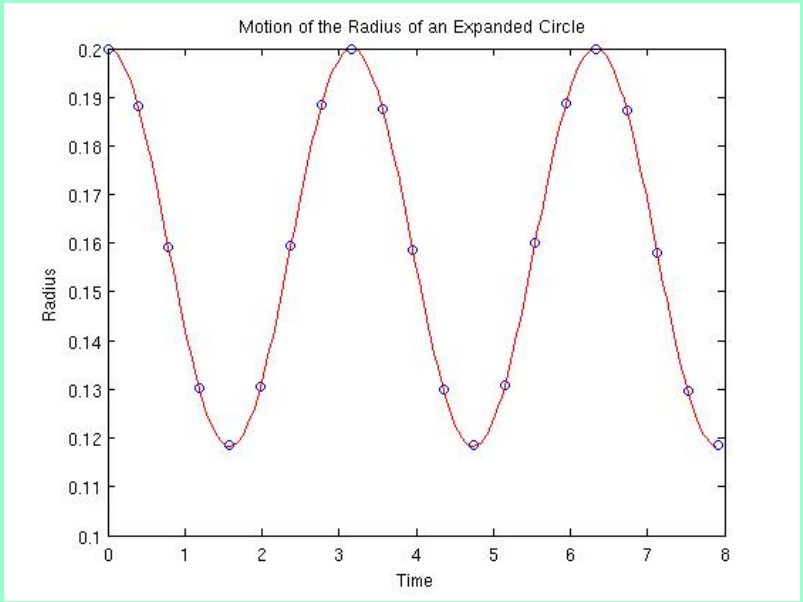
Membrane

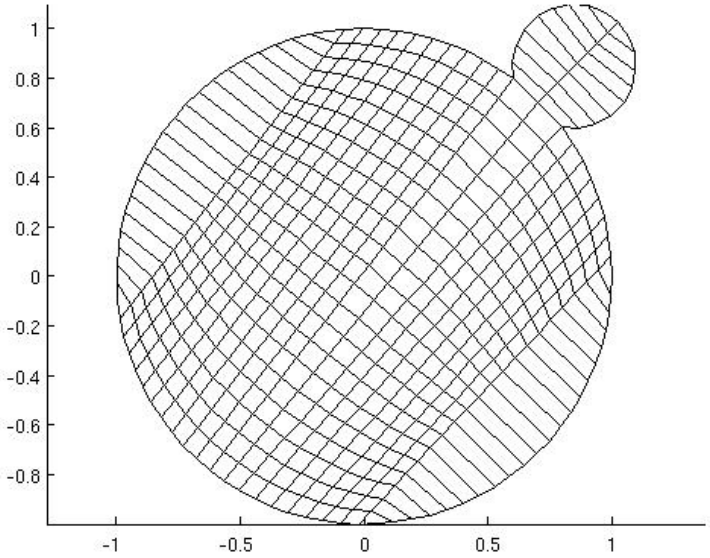
$$ma = E\varepsilon_S + \Delta p \cdot n$$

Validation of Elastic Motion

- Test elastic behavior of filaments and membrane against analytical solutions



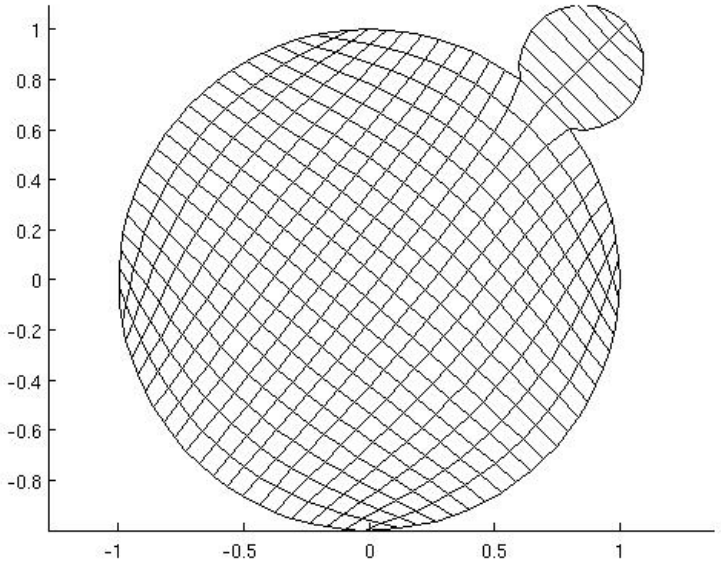


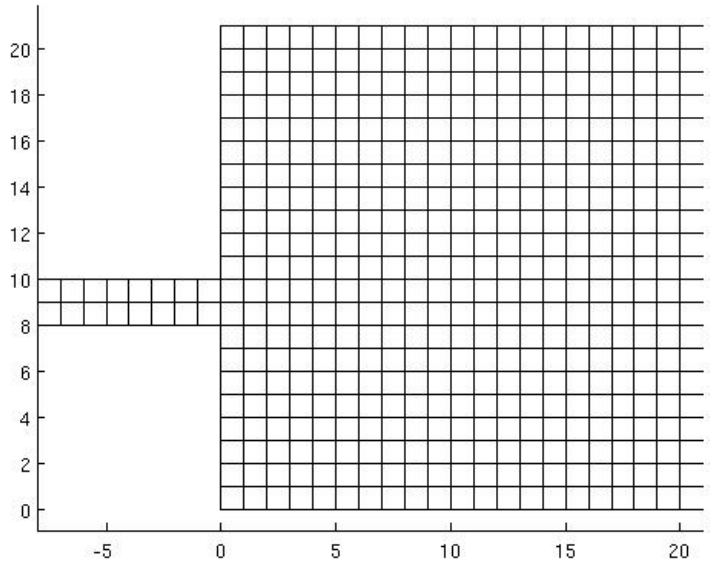


Validation of Orthogonal Grid Mapping

Physical Grids

Computational Grid





Outline of Simulation Time Step

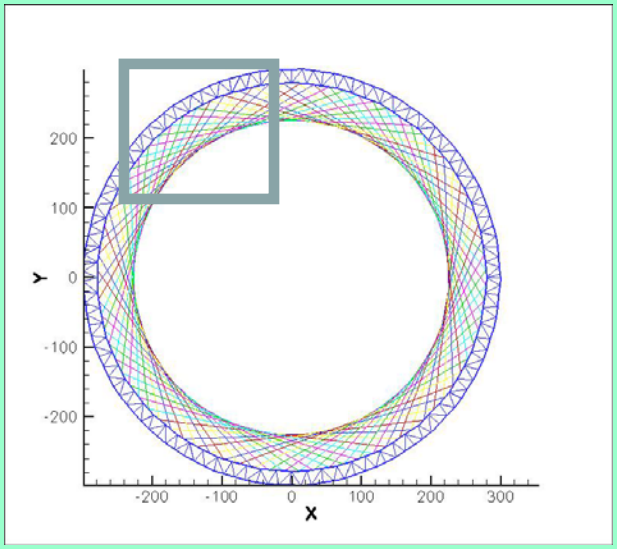
1. Fluid problem is solved
2. Pressures and velocities are stored
3. Filaments are moved using the fluid velocities
4. Filament endpoint forces are computed and stored

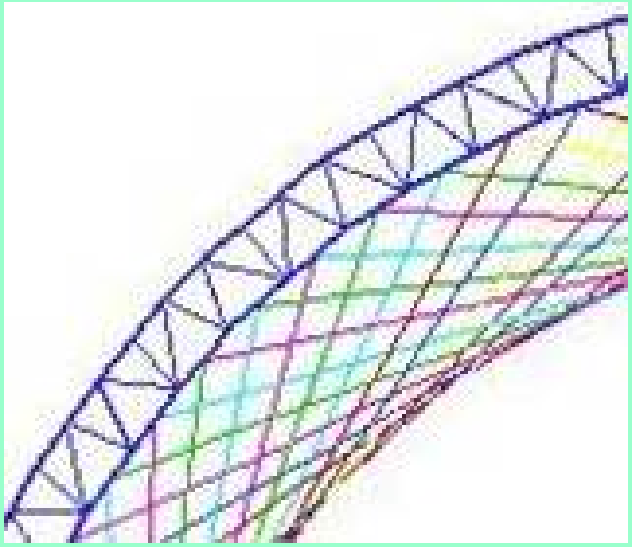
Outline of Simulation (cont)

5. Elasticity equations are solved, with the fluid pressures, filament tensions, exterior uniform pressure acting as external forces on the membrane
6. Displacement of the membrane updates the position of the fluid in the cell.
7. The process begins all over again!

Set-up for Simulation

- Higher pressure inside the cell than out
- Filaments begin in stretched states
- To simulate the formation of a bleb:
  - Break connections between filaments and membrane in one small region of the cell
  - Watch system evlove

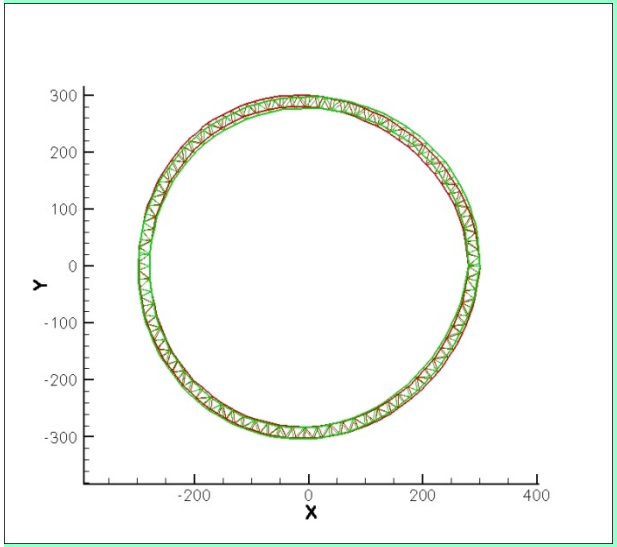


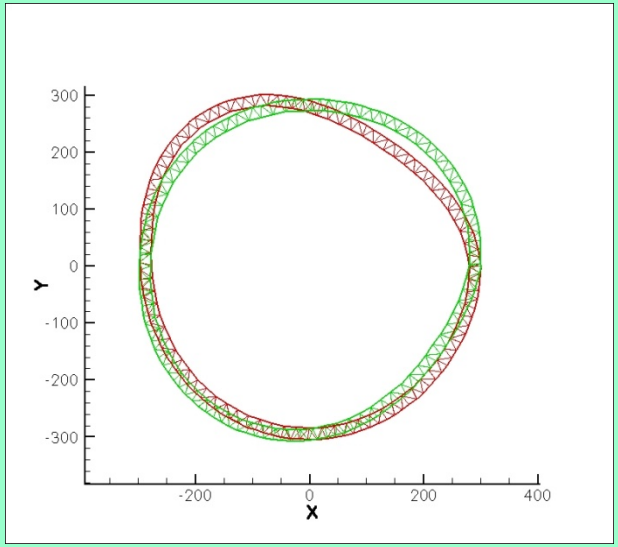


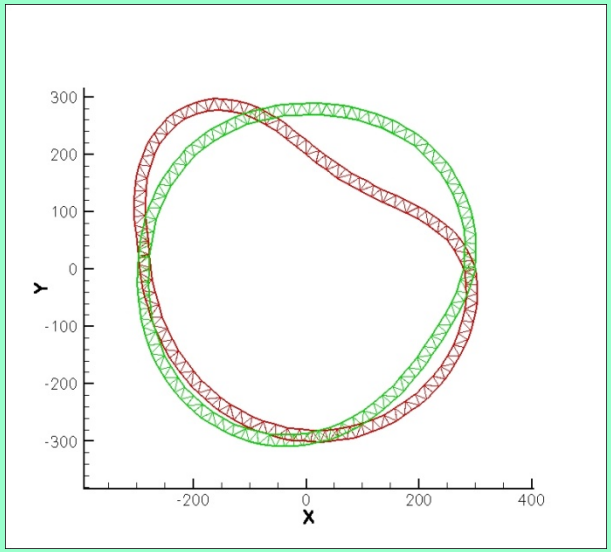
Past Results: Bleb Test

Green = Normal

Red = Broken Connections in upper left corner



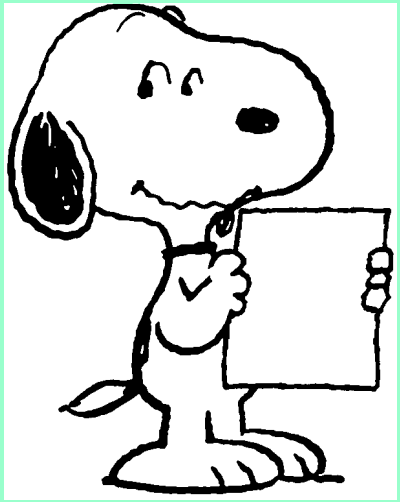




- Approx. 1/9 of filament connections broken

Future Direction

- Complete fluid-structure interaction for bleb simulation
- Addition of filament-filament interactions to simulate cytoskeletal mesh



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